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(54) Title: MODULATION OF SUBSTANCE P BY GABA ANALOGS AND METHODS RELATING THERETO

(57) Abstract

Modulation of substance P by GABA analogs is disclosed. Preferred GABA analog compounds include gabapentin and pregabalin. Methods of this invention include the modulation of substance P, as well as methods for preventing or treating conditions associated with substance P, by administering to an animal an effective amount of one or more GABA analog compounds. Conditions associated with substance P include headaches and migraine, neurogenic inflammation, emesis, nausea and vomiting, cough and bronchitis, obesity, allergy, asthma, hemorrhoids and anal fissures, ulcer, fever, infertility and periodontal disease.

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MODULATION OF SUBSTANCE P BY GABA ANALOGS AND METHODS RELATING THERETO

FIELD OF THE INVENTION

The present invention relates generally to a method of modulating substance P by gamma-aminobutyric acid (GABA) analog compounds, particularly gabapentin and pregabalin, and more specifically, to the use of such compounds to treat a variety of conditions associated with substance P.

BACKGROUND OF THE INVENTION

Substance P, along with neurokinin A and neurokinin B, are members of the tachykinin family of mammalian regulatory peptides (Dockray, Gut Peptides: Biochemistry and Physiology, Walsh and Dockray, editors, Raven Press, Ltd, New York, NY, 1994:401-422). In 1931, substance P was the first of the gut neuropeptides to be discovered (von Euler and Gaddum, *J. Physiol.*, 1931;72:74-87). Nearly 40 years later, substance P was isolated and sequenced from bovine hypothalamus, and determined to be an undecapeptide (Chang and Leeman, *J. Biol. Chem.*, 1970;245:4784-4790; Chang and Leeman, *Nature*, 1971;232:86-87). More recently, multiple receptor subtypes (i.e., NK1, NK2 and NK3) for the various tachykinin neuropeptides have been cloned and sequenced, with substance P being considered the natural ligand for receptors of the NK1 subtype (Dockray, 1994:408-409).

More specifically, substance P is a pharmacologically-active neuropeptide that is produced in mammals and possesses a characteristic amino acid sequence (Chang et al., *Nature New Biol.*, 1971;232:86; D. F. Veber et al., U.S. Patent No. 4,680.283).

Substance P is stored in the secretory granules of substance P immunoreactive nerves, which are afferent, small diameter, unmyelinated polymodal, C-type fibers with dual functions. Upon orthodromic stimulation by noxious stimuli, substance P is released from the spinal tract for central

transmission of nociceptive information. A secondary function involves release of substance P and other neuropeptides from collateral nerve terminals and peripheral tissue following antidromic noxious stimulation, resulting in "neurogenic inflammation." Such peripheral release of substance P has been implicated as a neurogenic promoter of various inflammatory processes, including asthma, rhinitis, conjunctivitis, and inflammation of the skin and mucosa (see Bartold et al., *J. Periodontol*, 1994;65:1113-1121). Substance P has also been found to be a potent vasodilator and increases vascular permeability, and has pro-inflammatory effects on neutrophils, macrophages, mast cells, lymphocytes, and endothelial cells (Bartold et al., 1994, supra). In addition to the central and peripheral nervous system, substance P immunoreactive nerves, and thus substance P itself, have been found in a variety of different mammalian tissues, including smooth muscles of the arteries and veins, pulmonary, urinary and gastrointestinal tracts, basal ganglia, substantia nigra, striatonigral pathways, hypothalamus, retina, hair follicles, gingival tissues, prostate gland, and even in spermatozoa.

In short, distribution of substance P is nearly ubiquitous in mammalian tissues. This wide distribution is believed to be due, at least in part, to the association of substance P (either directly or indirectly) with numerous processes and/or conditions. Substance P is capable of producing both analgesia and hyperalgesia in animals, depending on dose and pain responsiveness of the animal (see R. C. A. Frederickson et al., *Science*, 1978;199:1359; P. Oehme et al., *Science*, 1980;208:305) and plays a role in sensory transmission and pain perception (T. M. Jessell, *Advan. Biochem. Psychopharmacol.*, 1981;28:189). For example, substance P is believed to be involved in the neurotransmission of pain sensations [Otsuka et al, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 Substance P in the Nervous System, Ciba Foundation Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" TIPS, 8 506-510 (December 1987)], specifically in the transmission of pain in migraine (see B. E. B. Sandberg et al., *Journal of Medicinal Chemistry*, 1982;25:1009; M. A. Moskowitz, *Trends Pharmacol. Sci.*, 1992;13:307-311), and in arthritis (Levine, et al., *Science*, 1984;226:547-549; M. Lotz, et al., *Science*, 1987;235:893-895).

Tachykinins have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract, such as inflammatory bowel disease [see Mantyh et al., *Neuroscience*, 1988;25(3):817-837) and D. Regoli in "Trends in Cluster Headache" Ed. F. Sicuteri et al., Elsevier Scientific Publishers, Amsterdam, 1987:85-95], and emesis [*Trends Pharmacol. Sci.*, 1988;9:334-341, F. D. Tatersall et al., *Eur. J. Pharmacol.*, 1993;250:R5-R6].

It is also hypothesized that there is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd et al., "A Neurogenic Mechanism for Symmetric Arthritis" in *The Lancet*, 11 Nov. 1989 and Gronblad et al., "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in *J. Rheumatol.*, 1988;15(12):1807-10]. Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis [O'Byrne et al., *Arthritis and Rheumatism*, 1990;33:1023-1028]. Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases, proliferative vitreoretinopathy, irritable bowel syndrome and disorders of bladder function including cystitis and bladder detruser hyperreflexia is reviewed in "Tachykinin Receptors and Tachykinin Receptor Antagonists," C. A. Maggi, R. Patacchini, P. Rovero and A. Giachetti, *J. Auton. Pharmacol.*, 1993;13,23-93; see also R. M. Snider et al., *Chem. Ind.*, 1991;11:792-794. Neurokinin-1 receptor antagonists alone or in combination with bradykinin receptor antagonists may also be useful in the prevention and treatment of inflammatory conditions in the lower urinary tract, especially cystitis [Giuliani et al., *J. Urology*, 1993;150:1014-1017]. Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet et al., *Can. J. Pharmacol. Physiol.*, 1988;66:1361-1367], immunoregulation [Lotz et al., *Science*, 1988;241:1218-1221, Kimball et al., *J. Immunol.*, 1988;141(10):3564-3569; A. Perianin et al., *Biochem. Biophys. Res. Commun.*, 1989;161:520], post-operative pain and nausea [C. Bountra et al.,

Eur. J. Pharmacol., 1993;249:R3-R4, F. D. Tattersall et al., *Neuropharmacology*, 1994;33:259-260], vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh et al., *PNAS*, 1988;85:3235-3239] and, possibly by arresting or slowing beta -amyloid-mediated neurodegenerative changes [Yankner et al., *Science*, 1990;250:279-282] in senile dementia of the Alzheimer type, Alzheimer's disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Luber-Narod et. al., poster C.I.N.P. XVIIIth Congress, 28th June-2nd July, 1992], and in disorders of bladder function such as bladder detrusor hyper-reflexia [Lancet, 16th May 1992, 1239]. Antagonists selective for the neurokinin-1 (NK-1) and/or the neurokinin-2 (NK-2) receptor may be useful in the treatment of asthmatic disease (Frossard et al., *Life Sci.*, 1991;49:1941-1953; Advenier et al., *Biochem. Biophys. Res. Comm.*, 1992;184(3):1418-1424; P. Barnes et al., *Trends Pharmacol. Sci.*, 1993;11:185-189). Tachykinin antagonists may also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC) [Langdon et al., *Cancer Research*, 1992;52:4554-4557].

It has furthermore been suggested that tachykinin receptor antagonists have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophillic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorder related to immune enhancement or suppression such as systemic lupus erythmatosus (EPO Publication No. 0,436,334), ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like, and cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis (EPO Publication No. 0,394,989).

Substance P antagonists may be useful in mediating neurogenic mucus secretion in mammalian airways and hence provide treatment and symptomatic relief in diseases characterized by mucus secretion, in particular, cystic fibrosis [S. Ramnarine et al., abstract presented at 1993 ALA/ATS Int'l Conference, 16-19 May 1993, published in *Am. Rev. of Respiratory Dis.*, May 1993].

Administration of agents which modulate substance P would have significant utility over a wide range of disorders or conditions associated with substance P. For example, such agents would have utility in preventing and/or treating pain, neurogenic inflammation, headaches, migraine, neurological disorders, respiratory disorders, blood pressure, hematopoiesis, allergies, asthma, arthritis, irritable bowel syndrome, hemorrhoids, anal fissures, ulcerative colitis, Crohn's disease, proctitis, benign prostatic hypertrophy (BPH), cystitis, skin disorders, CNS disorders (such as Parkinson's disease, MS and Alzheimer's disease), as well as infertility, emesis, cough, bronchitis, osteoporosis, ulcers, fever and obesity. In this regard, it has been suggested that an ideal agent would have the ability to resist peptidases, and have the ability to enter the CNS (Lembeck, *Ann. N.Y. Acad. Sci.*, 1991;632:490-493).

Accordingly, there is a need in the art for agents which modulate substance P, as well as methods related to the use of such agents to prevent and/or treat conditions associated with substance P. The present invention fulfills these needs, and provides further related advantages.

SUMMARY OF THE INVENTION

Briefly stated, the present invention discloses compounds which modulate substance P, and methods for the use thereof. In the context of this invention, such compounds are GABA analogs, and are hereinafter referred to as "GABA analog compounds." Preferred GABA analog compounds of this invention include, but are not limited to, gabapentin and pregabalin.

The GABA analog compounds of the present invention have utility as substance P modulating agents, as well as in the prevention and/or treatment of a wide variety of conditions associated with substance P. Thus, in one embodiment, a GABA analog compound of this invention is administered to a warm-blooded animal in need thereof to modulate substance P. In another embodiment, a GABA analog compound is administered to a warm-blooded animal in need thereof to prevent and/or treat a condition associated with substance P.

In a further embodiment of this invention, a GABA analog compound is administered to the oral cavity of a warm-blooded animal to prevent and/or inhibit pain, neurogenic inflammation, headaches, migraines, neurological disorders, respiratory disorders, blood pressure, hematopoiesis, allergies, asthma, arthritis, irritable bowel syndrome, hemorrhoids, anal fissures, ulcerative colitis, Crohn's disease, proctitis, benign prostatic hypertrophy, cystitis, skin disorders, and CNS disorders (such as Parkinson's disease, multiple sclerosis and Alzheimer's disease), as well as infertility, emesis, cough, bronchitis, osteoporosis, ulcers, fever and obesity.

In yet a further embodiment, a GABA analog compound is administered to a warm-blooded animal to prevent and/or treat pain, neurogenic inflammation, headaches, migraines, neurological disorders, respiratory disorders, blood pressure, hematopoiesis, allergies, asthma, arthritis, irritable bowel syndrome, hemorrhoids, anal fissures, ulcerative colitis, Crohn's disease, proctitis, benign prostatic hypertrophy, cystitis, skin disorders, and CNS disorders (such as Parkinson's disease, multiple sclerosis and Alzheimer's disease), as well as infertility, emesis, cough, bronchitis, osteoporosis, ulcers, fever and obesity.

Other aspects of the present invention will become evident upon reference to the detailed description. To this end, certain references are listed herein for purpose of illustration and reference, and are incorporated herein by reference in their entirety.

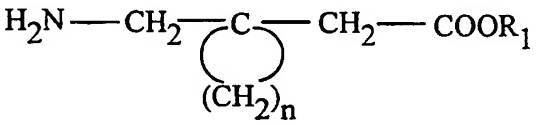
DETAILED DESCRIPTION OF THE INVENTION

As mentioned above, this invention is generally directed to compounds that are analogs of GABA (referred to herein as "GABA analog compounds"). Such GABA analog compounds modulate substance P, and therefor have utility as modulating agents of substance P, as well as in the prevention and/or treatment of a wide variety of conditions associated with substance P in warm-blooded animals, including humans.

As used herein, the term "conditions" includes diseases, injuries, disorders, indications and/or afflictions which are associated with substance P. Conditions

"associated with substance P" are those conditions which result, either directly or indirectly, from release of substance P and/or abnormally high levels of substance P. The term "treat" or "treatment" means that the symptoms associated with one or more conditions associated with substance P are alleviated or reduced in severity or frequency, and the term "prevent" means that subsequent occurrence of such symptoms are avoided or that the frequency between such occurrences is prolonged. The phrase "modulate substance P" means that substance P is regulated, adjusted, or adapted to a desired degree. For example, modulation of substance P may involve the prevention, inhibition or antagonization of substance P release, or that substance P, once released, is bound, complexed, impaired, scavenged or otherwise removed or affected as a causative agent of the condition.

A GABA analog compound of this invention is a compound of the following Formula I



I

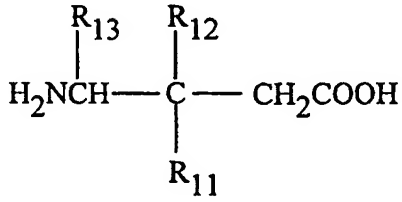
wherein R_1 is hydrogen or a lower alkyl; n is an integer of from 4 to 6; and the cyclic ring is optionally substituted, and the individual diastereomeric or enantiomeric isomers thereof; and the pharmaceutically acceptable salts thereof. The term lower alkyl includes straight or branched chain alkyl groups of up to 8 carbon atoms. An especially preferred embodiment utilizes a compound of Formula I where R_1 is hydrogen and n is 5, which compound is 1-(aminomethyl)-cyclohexane acetic acid, known generically as gabapentin.

Other preferred compounds of Formula I above include, but are not limited to, ethyl 1-aminomethyl-1-cyclohexane-acetate, 1-aminomethyl-1-cycloheptane-acetic acid, 1-aminomethyl-1-cyclopentane-acetic acid, methyl-1-aminomethyl-1-cyclohexane-acetate, n-butyl 1-aminomethyl-1-cyclohexane-acetate, methyl 1-aminomethyl-1-cycloheptane-acetate, n-butyl 1-aminomethyl-1-cycloheptane-acetate, toluene sulfonate, 1-aminomethyl-1-cyclopentane-acetate, benzene-sulfonate, and n-butyl 1-aminomethyl-1-cyclopentane-acetate.

Other preferred compounds of Formula I above, wherein the cyclic ring is substituted for example with alkyl such as methyl or ethyl, include, but are not

limited to (1-aminomethyl-3-methylcyclohexyl)acetic acid, (1-aminomethyl-3-methylcyclopentyl)acetic acid, and (1-aminomethyl-3,4-dimethylcyclopentyl)acetic acid.

In another preferred embodiment of the present invention, a GABA analog compound is a compound of the following Formula II



II

wherein R_{11} is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl having from 3 to 6 carbon atoms; R_{12} is hydrogen or methyl; and R_{13} is hydrogen, methyl, or carboxyl; and individual diastereomeric or enantiomeric isomers thereof; and pharmaceutically acceptable salts thereof.

The most preferred compound of Formula II is where R_{12} and R_{13} are both hydrogen, and R_{11} is -(CH_2)0-2-iC_4H_9 as an (R), (S), or (R,S) isomer. A more preferred embodiment of the invention utilizes 3-aminomethyl-5-methyl-hexanoic acid, and especially (S)-3-(aminomethyl)-5-methylhexanoic acid, now known generically as pregabalin. Another preferred compound is 3-(1-aminoethyl)-5-methylhexanoic acid.

While the GABA analog compounds of the present invention have been disclosed individually above, it should be understood that this invention encompasses compositions of two or more GABA analog compounds, as well as compositions containing at least one GABA analog compound in combination with other organic and/or inorganic constituents and/or other active constituents.

The GABA analog compounds of this invention have been found to modulate substance P. As mentioned above, substance P is an undecapeptide and a member of the tachykinin class of neuropeptides. Substance P is found in secretory granules of sensory neurons which are designated as substance P immunoreactive ("SP-IR") nerves. The primary function of the SP-IR nerves are for nociceptive information which, upon stimulation by noxious stimuli, release substance P and thereby mediate pain perception, for example, chronic pain or that

attributable to or associated with any of the foregoing conditions especially the transmission of pain in migraine, or such as headache, toothache, cancerous pain, back pain, and superficial pain on congelation, burn, herpes zoster or diabetic neuropathy. However, release of substance P and other neuropeptides from collateral nerve terminals and peripheral tissues result in neurogenic inflammation. Thus, the GABA analog compounds of this invention can be used to inhibit neurogenic inflammation by modulating substance P.

In addition, the GABA analog compounds of this invention may be used to prevent and/or treat a variety of conditions associated with substance P. SP-IR nerves, and thus substance P itself, are found in many different tissues, including the central and peripheral nervous system, smooth muscles of the arteries and veins, pulmonary, urinary and gastrointestinal tracts, basal ganglia, substantia nigra, striatonigral pathways, hypothalamus, retina, gingival tissue, prostate gland and even in spermatozoa. Due to its nearly ubiquitous distribution in mammalian tissue, substance P is believed to be associated with a variety of conditions. In addition to its involvement in pain mediation and promotion of neurogenic inflammation, substance P is associated with disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and other neuropathological disorders such as peripheral neuropathy, for example AIDS related neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, and postherpetic and other neuralgias; small cell carcinomas such as small cell lung cancer; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, acute bronchitis, diffuse panbronchilitis, emphysema, cystic fibrosis, asthma, and bronchospasm; laryngopharyngitis; bronchiectasis; conoisis; whooping cough; pulmonary tuberculosis; diseases associated with decreased glandular secretions, including lacrimation, such as Sjogren's syndrome, hyperlipoproteinemias IV and V, hemochromatosis, sarcoidosis, or amyloidosis; iritis; inflammatory diseases such as inflammatory bowel disease, inflammatory intestinal disease, psoriasis,

fibrositis, ocular inflammation, osteoarthritis, rheumatoid arthritis, pruritis, and sunburn; hepatitis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, dry eye syndrome, and the like; ophthalmic conditions associated with cell proliferation such as proliferative vitreoretinopathy; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis; hemodialysis-associated itching; lichen planus; oedema, such as oedema caused by thermal injury; addiction disorders such as alcoholism; mental disease, particularly anxiety and depression; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; tenalgia attended to hyperlipidemia; postoperative neuroma, particularly of mastectomy; vulvar vestibulitis; amniogenesis; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression, such as systemic lupus erythmatosus; gastrointestinal (GI) disorders, including inflammatory disorders, and diseases of the GI tract, such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel syndrome, nausea, and emesis, including acute, delayed, post-operative, late-phase, and anticipatory emesis, such as emesis or nausea induced by for example chemotherapy, radiation, surgery, migraine, toxins, such as metabolic or microbial toxins, viral or bacterial infections, pregnancy, vestibular disorder, motion, mechanical stimulation, gastrointestinal obstruction, reduced gastrointestinal motility, visceral pain, psychological stress or disturbance, high altitude, weightlessness, opioid analgesics, intoxication, resulting for example from consumption of alcohol, and variations in intercranial pressure, in particular, for example, drug or radiation induced emesis or post-operative nausea and vomiting; disorders of bladder function such as cystitis, bladder detrusor hyperreflexia, and incontinence; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease. Hence, these compounds may be readily adapted to therapeutic use for the treatment of physiological disorders associated with substance P, and as substance P or neurokinin-1 antagonists in the control

and/or treatment of any of the aforesaid clinical conditions in mammals, including humans.

The compounds of the present invention are also of value in the treatment of a combination of the above conditions.

The ability of the GABA analog compounds of this invention to modulate substance P may be assayed by known techniques, such as those disclosed by Mizrahi et al. (*Eur. J. Pharmacol.*, 1983;91:139-140) and Holzer et al. (*P. Eur. J. Pharmacol.*, 1983;91:83-88). For example, PanLabs Test Numbers 3-0580 screen the ability of compounds to function as substance P antagonists by determining the ability of the compound to inhibit substance P-induced contractions of guinea pig ileum.

Substance P plays a role in the release of various immunomodulatory cytokines produced by macrophages, such as tumor necrosis factor (TNF) and interleukin -1 (IL-1). Such cytokines induce release of prostaglandin E2 (PGE2) which plays a major role in the pathogenesis of bone and cartilage destruction in inflammatory diseases. Utility of the GABA analog compounds of this invention as immunomodulatory agents may be assayed by a number of commercially available techniques, including the techniques disclosed by Maloff et al. (*Clin. Chim. Acta.*, 1989;181:73-78). Representative assays include, for example, PanLabs Test Numbers 4-0140 and 4-0120 which screen agents for the ability to inhibit (or promote) PGE2 release from cells exposed to TNF and IL-1, respectively.

Similarly, the ability of the GABA analog compounds of this invention to bind to the neurokinin NK1 receptor may be determined by the procedure of Lee et al., *Mol. Pharmacol.*, 1983;23:563-569. In this assay, submaxillary glands are obtained from male guinea pigs and a membrane fraction prepared by standard techniques. The membrane preparation is then incubated with labeled substance P, and non-specific binding is estimated in the presence of the test compound. The membranes are then filtered and washed, and the filters are counted to determine bound, labeled substance P.

Fever is a defense mechanism which is regulated in the central nervous system and, more specifically, in the preoptic area of the anterior hypothalamus. This area has been known to play an important regulatory role in body

temperature (Blatteis et al., *Ann. of NY Acad. Sci.*, 1994;741:162-173). It is also known that substance P containing nerve cell terminals are present in the preoptic area of the anterior hypothalamus (Gallagher, *Brain Research Bull.*, 1992;20:199-207). In a guinea pig model of fever, IV injection of an exogenous pyrogen increased colonic temperature as measured using thermocouples. Substance P antagonist microinjected intrapreoptically attenuated the fevers showing that substance P inhibition results in reduced febrile response. In addition, when substance P was microinjected into the preoptic area of conscious guinea pigs, it caused an increase in temperature, whereas a substance P antagonist significantly attenuated the febrile response to IV pyrogen stimulation. Thus, the GABA analog compounds of this invention have activity in decreasing the febrile response in mammals.

It is postulated that release of sensory neuropeptides including substance P, neurokinin A and calcitonin-gene-related peptide may be one of the mechanisms of migraine pathogenesis (Buzzi et al., *Br. J. Pharmacology*, 1990;99:202-206). Moussaoiu et al., *European Journal of Pharmacology*, 1993;238:421-424) suggest that selective NK1 receptor antagonists could be greatly effective in humans for the treatment of migraine headaches. Capsaicin, a substance P inhibitor, was reported to decrease the severity of cluster headaches when administered intranasally to humans (Marks et al., *Cephalalgia*, 1993;13:114-116). Thus, the GABA analog compounds of this invention are useful in the treatment of migraine headaches, particularly via intranasal administration.

Impaired thermogenesis is thought to be the primary reason for obesity, although other mechanisms also play a role (Williams et al., *Clinical Sci.*, 1991;80:419-426). The hypothalamus is an important organ for control of food intake and thermogenesis. It contains over 50 putative neurotransmitters, among these substance P (Morely, *Endocrine Rev.*, 1987;8:257-287). High concentrations of substance P have been found in the ventro-medial hypothalamus which is the satiety center in mammalian species (Iverson, *Br. Med. Bull.*, 1982;38:277-282). Baroncenelli et al. (*Functional Neurology*, 1989;4:183-184) reported that plasma concentrations of substance P in obese children were significantly higher as compared to controls. They found a positive correlation between substance P

levels and percentage of weight gain. Thus, the GABA analog compounds of this invention may be used as weight loss agents modifying plasma substance P levels.

It is known that the mammalian stomach is widely innervated by capsaicin-sensitive afferent neurons (Shatkey et al., *Gastroenterology*, 1984;87:914-921). Substance P inhibitors, such as capsaicin, when given intragastrically prior to challenge with 30% ETOH, reduced the area of stomach injury. Substance P, when given IV, increased the areas of injury (Katori et al., *Regulatory Peptides*, 1993;46:241-243). It was further noted in the ulcerogenic rat model that the level of substance P in gastric fluid was increased significantly after challenge with 50% ETOH. In such a model of ulcerogenesis, the GABA analog compounds of this invention offer protection to the gastric mucosa, and thus may be used as a treatment for ulcers.

Vomiting and nausea occur in a wide variety of disorders such as peptic ulcer disease, peritonitis, acute systemic infections with fever, elevated intracranial pressure, morning sickness of early pregnancy, myocardial infarction and as a side effect of many drugs, ingested chemicals and anesthesia. Patients undergoing chemotherapy and radiation therapy for cancer also experience vomiting as a side effect. The nucleus tractus solitarius is the region in the brain where gastric vagal afferent fibers terminate, and this area is innervated by substance P-containing fibers (Otuska, *Physiology Review*, 1993;73:229). It has been suggested that substance P which is released by cytotoxic agents may induce emesis. It is also known that substance P is an emetic (Andrews et al., *Trends Pharmacol. Sci.*, 1988;9:334). Consequently, the GABA analog compounds of this invention are expected to attenuate emesis. In this context, the ferret model of induced emesis is commonly used to test antiemetic drugs (Tattersall, *European J. of Pharmacol.*, 1993;250:R5-R6; Knox et al., *Brain Research Bull.*, 1993;31:477-484).

Substance P is a neuropeptide known to cause coughing (Kohrogi, *Journal of Clinical Investigation*, 1998;82:2063-2068). In particular, substance P is known to activate the cough reflex and capsaicin has been used as a provocative agent to test the sensitivity of the cough reflex (Morice et al., *Lancet ii*, 1987:1116-1118). Karlsson (*Thorax*, 1993;48:396-400) suggests that there is a role for substance P sensitive nerves in chronic, non-productive cough and sneezing. Yoshihara et al.

(*Regulatory Peptides*, 1993;46:238-240) have reported that plasma substance P levels were higher in a pertussis group during the coughing stage than during the recovery stage or in the control group. In addition, it was also noted that the plasma substance P level decreased simultaneously with a decreasing number of coughing attacks. Thus, the GABA analog compounds of this invention may be used in the prevention and/or treatment of coughs of various etiologies.

Substance P immune reactive fibers have been localized in the anterior pituitary in the rat (Battmann et al., *J. Endocrinol.*, 1991;130:160-175) and in humans (Wormald et al, *J. Clin. Endocrinol. Matab.*, 1989;69:612-615). Substance Preceptors are present in ovaries (Wuttke, *Human Reproduction*, 1993;8(Suppl. 2):141-146) and in mouse and human testes (Chiwakta et al., *Endocrinology*, 1991;128:2441-2448). It has been reported that substance P may also be involved in the regulation of midcycle LH surges, and may be an important peptide in the regulation of reproductive events. It is also known that substance P is present in lactotrophs and gonadotropes in the rat anterior pituitary (Morel et al., *Neuroendocrinology*, 1982;35:86-92). The presence of substance P in these organs is apparently essential for reproduction. In addition, substance P may also play a role in the midcycle LH surge. Thus, the GABA analog compounds of this invention may be used to treat conditions of mammalian infertility.

Substance P neurons are found in afferent sensory branches of the trigeminal nerve which innervates the walls of the submucosal glands and blood vessels and the epithelium of the human nasal mucosa (Lundberg, *Am. Rev. Respir. Dis.*, 1987;137:S16-S23). Chaen et al. (*Ann. Otol. Rhinol. Laryngol.*, 1993;102:16-21) reported that substance P is actively secreted into the nose and may play an important role in nasal mucosa allergy reactions. Substance P is also reported to act as a mast cell secretagogue (Repke et al., *FEBS Letters*, 1987;221(2):236-240). It is known that substance P induces mucosecretion in human bronchi (Rogers et al., *European J. of Pharmacol.*, 1989;74:283-286). Braunstein et al. (*Am. Rev. Respir. Dis.*, 1991;144:630-635) reported that exogenously applied substance P causes an increase in nasal protein output in allergic rhinitis patients, and that substance P may play a role in allergic thiniris. Thus, the GABA analog compounds of this invention may be used to treat allergic

reactions such as allergic rhinitis, as well as other conditions in which there is nasal obstruction and/or abnormal mucus secretions, such as the common cold and acute and chronic bronchitis.

Accordingly, the GABA analog compounds of this invention are believed effective in preventing and/or treating the above conditions due to their ability to modulate substance P. To this end, the GABA analog compounds of the present invention may be utilized for pharmaceutical, prophylactic and/or cosmetic purposes, and are administered to a warm-blooded animal in an effective amount to achieve a desired result. In the case of pharmaceutical administration, an effective amount is a quantity sufficient to treat the symptoms of a condition and/or the underlying condition itself. An effective amount in the context of prophylactic administration means an amount sufficient to avoid or delay the onset of a condition and/or its symptoms. Lastly, an effective amount with regard to cosmetic administration is an amount sufficient to achieve the desired cosmetic result.

The pharmaceutical compositions of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains one or more of the compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid,

magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the compositions of the present invention may be incorporated for administration orally or by injection include aqueous solution, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

For the treatment of the clinical conditions and diseases noted above, the compounds of this invention may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

The compounds of this invention may be administered to patients (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. The dose will vary from patient to patient depending upon the nature and severity of disease, the patient's weight, special diets then being followed by a patient, concurrent medication, and other factors which those skilled in the art will recognize.

In the treatment of a condition associated with substance P, an appropriate dosage level will generally be about 0.001 to 50 mg per kg patient body weight per day which may be administered in single or multiple doses. Preferably, the dosage level will be about 0.01 to about 25 mg/kg per day; more preferably about 0.05 to about 10 mg/kg per day. For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.05 to 10 mg/kg per day, and especially about 0.1 to 5 mg/kg per day. A compound may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day. In the treatment

of emesis using an injectable formulation, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. A compound may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

The following examples are offered by way of illustration, and not by way of limitation.

EXAMPLES

TACHYKININ ANTAGONISM ASSAY

The compounds of this invention are useful for modulating substance P in the treatment of gastrointestinal disorders, central nervous system disorders, inflammatory diseases, pain or migraine and asthma in a mammal in need of such treatment. This activity can be demonstrated by the following assay.

A. Receptor Expression in COS

To express the cloned human neurokinin-1 receptor (NK1R) transiently in COS, the cDNA for the human NK1R was cloned into the expression vector pCDM9 which was derived from pCDM8 (INVITROGEN) by inserting the ampicillin resistance gene (nucleotide 1973 to 2964 from BLUESCRIPT SK +) into the Sac II site. Transfection of 20 μg of the plasmid DNA into 10 million COS cells was achieved by electroporation in 800 μL of transfection buffer (135 mM NaCl, 1.2 mM $CaCl_2$, 1.2 mM $MgCl_2$, 2.4 mM K_2HPO_4, 0.6 mM KH_2PO_4, 10 mM glucose, 10 mM HEPES pH 7.4) at 260 V and 950 μF using the IBI GENEZAPPER (IBI, New Haven, CT). The cells were incubated in 10% fetal calf serum, 2 mM glutamine, 100 μ/mL penicillin-streptomycin, and 90% DMEM media (GIBCO, Grand Island, NY) in 5% CO_2 at 37°C for 3 days before the binding assay.

B. Stable Expression in CHO

To establish a stable cell line expressing the cloned human NK1R, the cDNA was subcloned into the vector pRcCMV (INVITROGEN). Transfection of

20 μg of the plasmid DNA into CHO cells was achieved by electroporation in 800 μL of transfection buffer supplemented with 0.625 mg/mL Herring sperm DNA at 300 V and 950 μF using the IBI GENEZAPPER (IBI). The transfected cells were incubated in CHO media [10% fetal calf serum, 100 U/mL pennicilin-streptomycin, 2 mM glutamine, 1/500 hypoxanthine-thymidine (ATCC), 90% IMDM media (JRH BIOSCIENCES, Lenexa, KS), 0.7 mg/mL G418 (GIBCO)] in 5% CO_2 at 37°C until colonies were visible. Each colony was separated and propagated. The cell clone with the highest number of human NK1R was selected for subsequent applications such as drug screening.

C. Assay Protocol using COS or CHO

The binding assay of human NK1R expressed in either COS or CHO cells is based on the use of <125> I-substance P (<125> I-Sp, from DU PONT, Boston, MA) as a radioactively labeled ligand which competes with unlabeled substance P or any other ligand for binding to the human NK1R. Monolayer cell cultures of COS or CHO were dissociated by the non-enzymatic solution (SPECIALTY MEDIA, Lavallette, NJ) and resuspended in appropriate volume of the binding buffer (50 mM Tris pH 7.5, 5 mM $MnCl_2$, 150 mM NaCl, 0.04 mg/mL bacitracin, 0.004 mg/mL leupeptin, 0.2 mg/mL BSA, 0.01 mM phosphoramidon) such that 200 μL of the cell suspension would give rise to about 10,000 cpm of specific <125> I-SP binding (approximately 50,000 to 200,000 cells). In the binding assay, 200 μL of cells were added to a tube containing 20 μL of 1.5 to 2.5 nM of <125> I-SP and 20 μL of unlabeled substance P or any other test compound. The tubes were incubated at 4°C or at room temperature for 1 hour with gentle shaking. The bound radioactivity was separated from unbound radioactivity by GF/C filter (BRANDEL, Gaithersburg, MD) which was pre-wetted with 0.1% polyethylenimine. The filter was washed with 3 mL of wash buffer (50 mM Tris pH 7.5, 5 mM $MnCl_2$, 150 mM NaCl) 3 times, and its radioactivity was determined by gamma counter.

The activation of phospholipase C by NK1R may also be measured in CHO cells expressing the human NK1R by determining the accumulation of inositol monophosphate which is a degradation product of IP3. CHO cells are

seeded in 12-well plate at 250,000 cells per well. After incubating in CHO media for 4 days, cells are loaded with 0.025 μCi/mL of <3> H-myoinositol by overnight incubation. The extracellular radioactivity is removed by washing with phosphate buffered saline. LiCl is added to the well at final concentration of 0.1 mM with or without the test compound, and incubation is continued at 37°C for 15 minutes. Substance P is added to the well at final concentration of 0.3 nM to activate the human NK1R. After 30 minutes of incubation at 37°C, the media is removed and 0.1N HCl is added. Each well is sonicated at 4°C and extracted with $CHCl_3$/methanol (1:1). The aqueous phase is applied to a 1 mL Dowex AG 1X8 ion exchange column. The column is washed with 0.1N formic acid followed by 0.025 M ammonium formate-0.1N formic acid. The inositol monophosphate is eluted with 0.2 M ammonium formate-0. 1N formic acid and quantitated by beta counter.

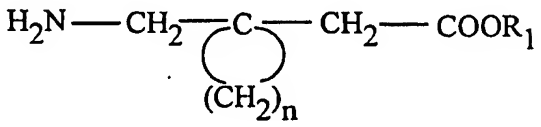
The activity of the present compounds may also be demonstrated by the assay disclosed by Lei et al., *British J. Pharmacol.*, 1992;105:261-262.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

CLAIMS

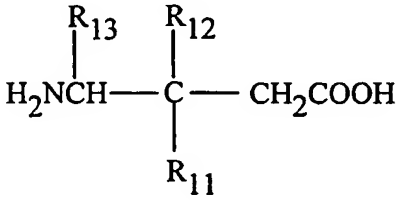
What is claimed is:

1. A method for inhibiting substance P in a warm-blooded animal, comprising administering to an animal in need thereof an effective amount of a GABA analog compound of structural formulas I and II:



I

wherein R_1 is hydrogen or a lower alkyl; n is an integer of from 4 to 6; and the cyclic ring is optionally substituted, and the individual diastereomeric or enantiomeric isomers thereof; and the pharmaceutically acceptable salts thereof.



II

wherein R_{11} is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl having from 3 to 6 carbon atoms; R_{12} is hydrogen or methyl; and R_{13} is hydrogen, methyl, or carboxyl; and individual diastereomeric or enantiomeric isomers thereof; and pharmaceutically acceptable salts thereof.

2. The method of Claim 1 wherein the GABA analog compound is administered within a composition further comprising at least one pharmaceutically acceptable carrier or diluent.

3. The method of Claim 2 wherein the GABA analog compound is present in the composition in an amount ranging from 0.05% to 50% by weight of the composition.

4. The method of Claim 2 wherein the GABA analog compound is present in the composition in an amount ranging from 0.1% to 20% by weight of the composition.

5. The method of Claim 2 wherein the composition is administered topically.

6. The method of Claim 2 wherein the composition is administered systemically.

7. The method of Claim 2 wherein the composition is administered orally.

8. The method of Claim 2 wherein the composition is administered intranasally.

9. A method for reducing abnormally high levels of substance P in a warm-blooded animal, comprising administering to an animal in need thereof an effective amount of gabapentin.

10. The method of Claim 9 wherein the gabapentin is administered within a composition further comprising at least one pharmaceutically acceptable carrier or diluent.

11. The method of Claim 10 wherein the gabapentin is present in the composition in an amount ranging from 0.05% to 50% by weight of the composition.

12. The method of Claim 10 wherein the gabapentin is present in the composition in an amount ranging from 0.1% to 20% by weight of the composition.

13. The method of Claim 10 wherein the composition is administered topically.

14. The method of Claim 10 wherein the composition is administered systemically.

15. The method of Claim 10 wherein the composition is administered orally.

16. The method of Claim 10 wherein the composition is administered intranasally.

17. A method for reducing abnormally high levels of substance P in a warm-blooded animal, comprising administering to an animal in need thereof an effective amount of pregabalin.

18. The method of Claim 9 wherein the pregabalin is administered within a composition further comprising at least one pharmaceutically acceptable carrier or diluent.

19. The method of Claim 10 wherein the pregabalin is present in the composition in an amount ranging from 0.05% to 50% by weight of the composition.

20. The method of Claim 10 wherein the pregabalin is present in the composition in an amount ranging from 0.1% to 20% by weight of the composition.

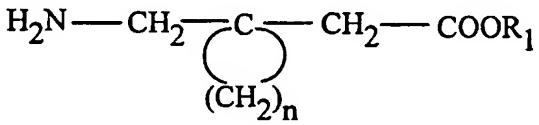
21. The method of Claim 10 wherein the composition is administered topically.

22. The method of Claim 10 wherein the composition is administered systemically.

23. The method of Claim 10 wherein the composition is administered orally.

24. The method of Claim 10 wherein the composition is administered intranasally.

25. A method for the treatment or prevention of a condition selected from the group consisting of: headaches, respiratory disorders, blood pressure, hematopoiesis, allergies, asthma, irritable bowel syndrome, hemorrhoids, anal fissures, ulcerative colitis, Crohn's disease, proctitis, benign prostatic hypertrophy, cystitis, skin disorders, infertility, emesis, cough, bronchitis, osteoporosis, ulcers, fever and obesity, in a mammal in need thereof which comprises the administration to the mammal of an effective amount of a compound of structural Formula I

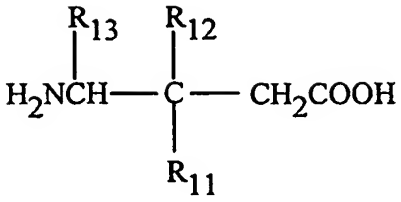


I

wherein R_1 is hydrogen or a lower alkyl; n is an integer of from 4 to 6; and the cyclic ring is optionally substituted, and the individual diastereomeric or enantiomeric isomers thereof; and the pharmaceutically acceptable salts thereof.

26. The method of Claim 25 wherein the compound is gabapentin.

27. A method for the treatment or prevention of a condition selected from the group consisting of: headaches, respiratory disorders, blood pressure, hematopoiesis, allergies, asthma, irritable bowel syndrome, hemorrhoids, anal fissures, ulcerative colitis, Crohn's disease, proctitis, benign prostatic hypertrophy, cystitis, skin disorders, infertility, emesis, cough, bronchitis, osteoporosis, ulcers, fever and obesity, in a mammal in need thereof which comprises the administration to the mammal of an effective amount of a compound of structural Formula II



II

wherein R_{11} is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl having from 3 to 6 carbon atoms; R_{12} is hydrogen or methyl; and R_{13} is hydrogen, methyl, or carboxyl; and individual diastereomeric or enantiomeric isomers thereof; and pharmaceutically acceptable salts thereof.

28. The method of Claim 25 wherein the compound is pregabalin.

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WO 00/67742 A3

(54) Title: USE OF GABA ANALOGUES FOR THE MODULATION OF SUBSTANCE P

(57) Abstract: Modulation of substance P by GABA analogs is disclosed. Preferred GABA analog compounds include gabapentin and pregabalin. Methods of this invention include the modulation of substance P, as well as methods for preventing or treating conditions associated with substance P, by administering to an animal an effective amount of one or more GABA analog compounds. Conditions associated with substance P include headaches and migraine, neurogenic inflammation, emesis, nausea and vomiting, cough and bronchitis, obesity, allergy, asthma, hemorrhoids and anal fissures, ulcer, fever, infertility and periodontal disease.

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/US 00/06199

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PARTRIDGE BRETT J ET AL: "Characterization of the effects of gabapentin and 3-isobutyl-gamma-aminobutyric acid on substance P-induced thermal hyperalgesia." ANESTHESIOLOGY (HAGERSTOWN), vol. 88, no. 1, January 1998 (1998-01), pages 196-205, XP000979389 ISSN: 0003-3022 the whole document ---	1-28
X	WO 98 03167 A (SINGH LAKHBIR ;WARNER LAMBERT CO (US)) 29 January 1998 (1998-01-29) the whole document ---	1-28
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

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'P' document published prior to the international filing date but later than the priority date claimed

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'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 March 2001	14/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Orviz Diaz, P

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INTERNATIONAL SEARCH REPORT

Im ational Application No
PCT/US 00/06199

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WETZEL C H ET AL: "Use of gabapentin in pain management" ANNALS OF PHARMACOTHERAPY,XX,XX, vol. 31, no. 9, September 1997 (1997-09), pages 1082-1083, XP002101739 ISSN: 1060-0280 the whole document	1-28
X	FIELD M J ET AL: "GABAPENTIN (NEURONTIN) AND S-(+)-3-ISOBUTYLGABA REPRESENT A NOVEL CLASS OF SELECTIVE ANTIHYPERALGESIC AGENTS" BRITISH JOURNAL OF PHARMACOLOGY,GB,BASINGSTOKE, HANTS, vol. 121, no. 8, 1997, pages 1513-1522, XP002043785 ISSN: 0007-1188 the whole document	1-28
A	BRYANS JUSTIN S ET AL: "3-substituted GABA analogs with central nervous system activity: A review." MEDICINAL RESEARCH REVIEWS, vol. 19, no. 2, March 1999 (1999-03), pages 149-177, XP000979391 ISSN: 0198-6325 the whole document	1-28

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The independent claims 1, 9 and 17 refer to the use of certain GABA derivatives for inhibiting substance P. This definition is not clear, because it is not possible to conclude unequivocally from this wording alone what specific therapeutic indications are meant.

A list of possible indications related to this mechanism of action is given in claims 25 and 27. Although some references in the description allegely support the involvement of Substance P in some of these diseases, the potential usefulness of substance P inhibitors in their treament is highly speculative. Furthermore, the description does not support any medical indication of the GABA derivatives of claim 1. Consequently, a complete search covering all these otherwise unrelated indications is not possible. The search was limited to the general mechanism of action and to the most widely accepted potential usefulness of substance P inhibitors, the tretament of pain.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In. ational Application No
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